

REMARKS

This is in response to the Office Action dated April 20, 2005 in connection with the above application. Issues raised in the Office Action are addressed below in the order they were raised by the Examiner.

Rejection of Claims 2, 9-12, 16, 20, and 24-25 under 35 USC § 103(a)

The Examiner has continued to reject claims 1-4, 8-11, and 14 under 35 USC § 103(a) as allegedly being unpatentable over Uchida et al. (U.S. Pat. No. 6,150,092) in view of Robinson et al. (WO 95/04142), Agrawal et al. (PNAS, Vol. 94:2620-2625, 1997), and Bennett et al. (U.S. Pat. No. 5,998,148). In particular, the Examiner has discounted the Declaration of Dr. Gill as allegedly providing merely an opinion and no material facts.

Applicants respectfully traverse. The opinions of experts in the field are highly relevant to an analysis of obviousness, particularly where those opinions are based on a reasoned analysis of the facts. A *prima facie* case of obviousness cannot be made unless one of ordinary skill in the art, at the time of filing, would have been motivated to modify Uchida's antisense probes, in particular, SEQ ID NO: 50 of Uchida, in both sequence and 2'O-methylation. The only possible motivation for making such modifications would be for the purpose of using the probes in vivo. The Examiner has proposed no other motivation. Therefore, a key is this: would one of ordinary skill in the art have been motivated by the information available in the art at the time of filing to modify the probes of Uchida et al. for use in vivo? The information provided by experts in the field is vitally important for answering this question.

The previously filed Declaration of Dr. Gill highlights the uncontested fact that the few probes that Uchida et al. tested in cells showed dramatically decreased efficacy relative to the efficacy observed in cell free assays. Uchida et al. used roughly fifty fold higher probe concentrations in the cell-based assays and observed roughly a ten fold decreased effect on VEGF expression relative to the cell free assays. Dr. Gill's Declaration further demonstrates that one of ordinary skill in the art would conclude from Uchida's data that the tested probes of Uchida et al. are not effective for inhibiting VEGF expression in cells.

In support of Dr. Gill's Declaration, Applicants enclose herewith **Exhibit A**, a copy of the Declaration of Dr. Ruiwen Zhang filed in the parent application (Ser. No. 09/487023). Dr. Zhang is another practitioner in the field of antisense. In sections 3, 4, and 5 of this Declaration, Dr. Zhang provides an analysis of Uchida et al. Dr. Zhang reaches the same conclusion as Dr. Gill. For example, Dr. Zhang's statement reads, "the antisense probes identified by Uchida et al. are not effective for inhibiting VEGF expression in cells. These data would not have motivated me to modify and test other probes disclosed by Uchida et al. for use in cells." See, e.g., Exhibit A page 3, lines 2-5. Applicants note that Dr. Zhang is not an inventor named in the present application and nor, to Applicants' knowledge, did Dr. Zhang participate in the invention of the claimed subject matter.

Therefore, two persons of skill in the relevant art have reviewed Uchida et al. and have concluded that the data from cell-based assays shows that the selected probes had no significant effect on VEGF expression in cells. Moreover, both experts have concluded that they would not have been motivated by Uchida's disclosure to select and modify additional probes from Uchida et al. for use in vivo.

Contrary to the Examiner's assertion, this information is highly relevant to the obviousness inquiry, regardless of whether the Examiner chooses to call it fact or opinion. Applicants have now provided the Declarations of two experts in the field, both reaching the same conclusion. Against this evidence, the Examiner has raised only his own opinion that Uchida's probes did in fact show meaningful efficacy in cells.

The weight of evidence clearly supports Applicants' position. Accordingly, reconsideration and withdrawal of the rejection under 35 USC § 103(a) are respectfully requested.

CONCLUSION

Applicants respectfully request reconsideration and withdrawal of the pending rejections. Applicants believe that the claims are now in condition for allowance and early notification to this effect is earnestly solicited. Any questions arising from this submission may be directed to the undersigned at (617) 951-7000. If there are any other fees due in connection with the filing of this submission, please charge the fees to our **Deposit Account No. 18-1945**, under VASG-P03-003.

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Respectfully Submitted,



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